



Collision between Two Pandemics: Obesity and COVID-19 Viral Infection

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the novel coronavirus disease 2019 (COVID-19). The principal risk factor for the development of serious forms of COVID-19 was found to be the precarious metabolic health. There are several mechanisms that are implicated in the seriousness of COVID-19 ranging from attenuation of immune system function to chronic inflammation. It is important to keep in mind that obesity is a complex disease when discussing the relation between obesity and the severity of COVID-19. An increasing body of proof links obesity to COVID-19. Obesity has an obvious role in the high incidence, symptoms severity and mortality rates of viral infections seen in obese patients. Adipose tissue shows a high expression of the angiotensin-converting enzyme 2 (ACE2), the receptor for entry of SARS-CoV-2 into host cells, so obese population exhibit higher vulnerability to COVID-19. The primary immune response is offered mainly by type-I interferon (IFN-I) that is suppressed in COVID-19. The pro-inflammatory state associated with obesity produces imbalance of the inflammatory response to COVID-19, as the cytokine storm found in subjects with serious disease form. Obesity is considered as chronic inflammation of low degree, so it shows a capacity for pathogenic immune

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amplification. In this review, the effect of obesity on the immune system is described. The authors described the dysfunctional immune responses caused by obesity that lead to organ injury in COVID-19 infection and impair the ability of patient to combat the virus. Further research is required to assess the impact of obesity control, immunonutrition and physical exercise in SARS-CoV-2 infection.

Keywords: COVID-19; obesity; inflammation; oxidative stress; immune response.

1. INTRODUCTION

COVID-19 pandemic is caused by the influenza-like virus strain (SARS-CoV-2) [1,2]. A coronavirus outbreak in China called the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was recorded by the end of year 2019, rapidly spreading and infecting about 14 million people and was announced an International Public Service Health Emergency at the end of January, 2020 [2-4]. Contact with droplets that contain viral particles expelled by the infected person's cough or sneezing is the main mode of transmission and the incubation period typically ranges from two to fourteen days [3,4]. Around 80% of patients are asymptomatic or have mild symptoms and 20% may have severe symptoms, leading to death [5,6].

The severity of Coronavirus Disease 2019 depends on the interaction between the host's immune system and SARS-CoV-2. The immune response being influenced by nutritional and physical status of the patient [7-9].

The immune response is divided into two classes: innate immunity and adaptive immunity [10,11]. The innate immunity encloses chemical barriers and physical barriers as well as the action of special cells such as natural killer cells, dendritic cells, macrophages, neutrophils and molecules like interleukins (ILs), cytokines, superoxide anion (O_2^-) and nitric oxide (NO). The adaptive immunity comprises B lymphocytes and their products (like cytokines and antibodies) and T-lymphocytes (CD4+ & CD8+). It can also be classified into cellular immunity (cells-mediated as lymphocytes & macrophages) and humoral immunity (antibodies-mediated) [10,11].

It has been recognized that malnutrition is correlated with bad prognosis of viral infection since Spanish influenza pandemic of 1918 [12]. Obesity was also associated with an elevated risk of serious illness, hospitalization and death in 2009 during influenza A virus H1N1 pandemic [13]. Obesity is a major significant condition that raises the risk of mortality in patients with SARS-

CoV-2 exponentially [14]. A clear association of obesity and viral infection complications was formerly reported for both the influenza virus and the previous corona viruses, SARS and MERS [14-17]. Studies indicated that persons suffering from obesity are at higher risk of hospitalization regardless of the viral state. Moreover, obese subjects are at a higher risk of hospital admission when infected by influenza if compared to non-infected patients [18,19].

Therefore, this review describes the impact of obesity and dysfunctional adipose tissue on the immunity during fighting COVID-19. For this objective, the bibliographic review covered awareness of the impact of obesity on the immune response and knowledge on the immunopathogenesis of SARS-CoV-2 infection. To finish this review, a comprehensive electronic search of the medical articles published were carried out through databases including PubMed, Web of Science, google scholar.

2. EFFECT OF OBESITY ON IMMUNE SYSTEM

No one can deny that obesity is a huge problem in our lives. Its catastrophic effects have been identified in numerous areas of the human body but still its impact on the immune system is unparalleled with any other disease.

Obese individuals are in a low-grade chronic inflammatory state leading to systemic metabolic dysfunction [14]. Adipose tissue (AT) is a vital endocrine organ that secretes hormones such as adipokines (lipokines), extracellular vesicles, endocrine factors, enzymes [14,15]. AT can secrete a multitude of cell-signaling cytokines named adipokines that regulate both local and systemic inflammation [16-17].

In lean individuals, adipocytes are insulin-sensitive, an important feature for the adipocyte glucose uptake also for modulation of gluconeogenesis in liver, that allow normal blood glucose levels to be preserved [18].

Adipose tissue consists of adipocytes in addition to various stromal cells like mesenchymal stromal/stem cells that derived from adipose tissue, fibroblasts and various immune cells [19]. Approximately, immune cells like monocytes, resident macrophages, mast cells, natural killer cells, dendritic cells, T- and B-cells, eosinophils, and neutrophils have been shown in AT [20].

The composition, structure and function of adipose tissue are affected by obesity. AT undergoes expansion through two mechanisms: hyperplasia (increasing the numbers of adipocyte) and hypertrophy (increasing the size of adipocyte) in response to excessive calorie intake. Adipocyte expansion and inadequate vascularization contribute to hypoxia, apoptosis/necrosis of adipocyte, abnormal flux of fatty acid, inflammatory adipokine secretion, triggering a large invasion of immune cells that promotes the following: inflammation, lipolysis and insulin resistance, which in turn contributes to dysfunction of adipocytes [21]. Adipocyte dysfunction induces a local low-grade inflammatory state in adipose tissue that attracts B-cells, T-cells, neutrophils, M1 macrophages and mast cells. On the other hand, in obesity, T helper type 2, regulatory T-cells and M2 macrophages show no change or may decrease [15,22,23]. This shifts the regulatory anti-inflammatory immune status, which induces the production of immunoregulatory cytokines namely interleukin-4 (IL-4), IL-5, IL-10, IL-13 and IL-33, to a severe state of inflammation that induces production of tumor necrosis factor alpha (TNF- α), monocyte chemoattractant protein-1 (MCP-1), IL-1 β , IL-6, interferon gamma and induction of systemic chronic inflammations [24].

High levels of inflammatory cytokines TNF- α and IL-6 are mainly formed in obese AT by elevated M1 macrophages [25] and these disturbed levels have been recorded in overweight and obesity patients [26], leading to both local and systemic chronic inflammation. In addition, IL-6 trans-signaling recruits macrophages to adipose tissue [27]. M1 macrophages are classically activated, typically by IFN- γ or lipopolysaccharide and produce proinflammatory cytokines, phagocytize microbes, and initiate an immune response. M1 macrophages produce nitric oxide or reactive oxygen intermediates to protect against bacteria and viruses. M2 macrophages are alternatively activated by exposure to certain cytokines such as IL-4, IL-10, or IL-13. M2 macrophages will

produce either polyamines to induce proliferation or proline to induce collagen production. These macrophages are associated with wound healing and tissue repair [28]. Mauer et al. [28] have outlined the importance of IL-6 to polarize macrophages into the subtype M2 [28,29]. The two mechanisms are probably involved in inflammatory maladaptation of obese adipose tissue. Excessive amounts of cytokines like IL-6, IL-8, leptin, plasminogen activator inhibitor-1 (PAI-1) monocyte chemoattractant protein-1 (MCP-1/CCL2) are produced by dysfunctional hypertrophic adipocytes of obese individuals, leading to increased macrophage recruitment, especially polarized macrophages M1 subtype [30,31] (Fig. 1). In turn, viruses can induce the production of elevated levels of proinflammatory molecules such as IL-1 β , IL-6, IL-8, TNF- α and MCP-1 (Fig. 2). The elevated plasma levels of free fatty acids via the NF- κ B pathway enhances this effect [32,33]. In serious cases of COVID-19, the accumulated effect of these actions is a condition of hypercytokinemia and chronic inflammation, which results in impaired innate immunity and provides a good environment for the hyperinflammatory reaction produced by the Cytokine Storm "macrophage activation syndrome" [34].

3. HOW DOES THE VIRUS CAUSE ITS INFECTION?

SARS-CoV-2 contains four distinct types of structural proteins: spike, nucleocapsid, membrane and envelope proteins. Spike protein (S), which consists of 2 different subunits, S1 and S2, provides viral entry into host cells. The S1 subunit is responsible for binding the virus to the recipient of the host cell; while the S2 subunit is responsible for viral fusion with cell membranes. Angiotensin-Converting Enzyme 2 (ACE2) is the cellular receptor for the virus and is expressed in alveolar epithelial cells (type I and type II) in pulmonary tissues and other tissues like cardiac, renal, pancreatic and endothelial tissue [35]. The greater the expression of ACE2 in the cell membrane, the greater the infectivity. However, despite the decline in tissue ACE2 expression with age, elderly patients have greater severity of lung damage and higher lethality rate from COVID-19. This is supported by the fact that, with aging, there is greater activation of proinflammatory signaling pathways [36].

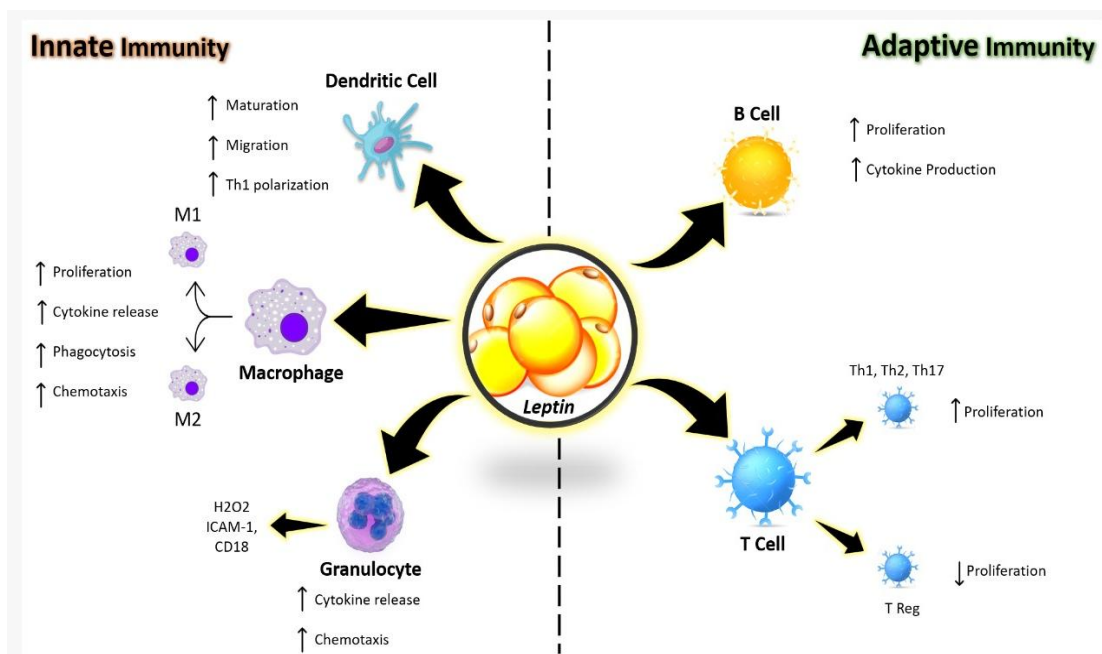


Fig. 1. Effect of leptin on immune system. Leptin regulates both innate and adaptive responses. In innate immunity, leptin increases the cytotoxicity of natural killer (NK) cells and promotes the activation of granulocytes, macrophages and DCs. Leptin regulates also M1- or M2-phenotype polarization and modulates DCs. In adaptive immunity, leptin increases the proliferation of naïve T cells and B cells while it reduces that of regulatory T cells (Treg). Leptin promotes the switch towards a pro-inflammatory Th1 (which secretes IFN γ) rather than anti-inflammatory Th2 (which secretes IL-4) phenotype and facilitates Th17 responses. Finally, leptin activates B cells to secrete cytokines and modulates B cell development

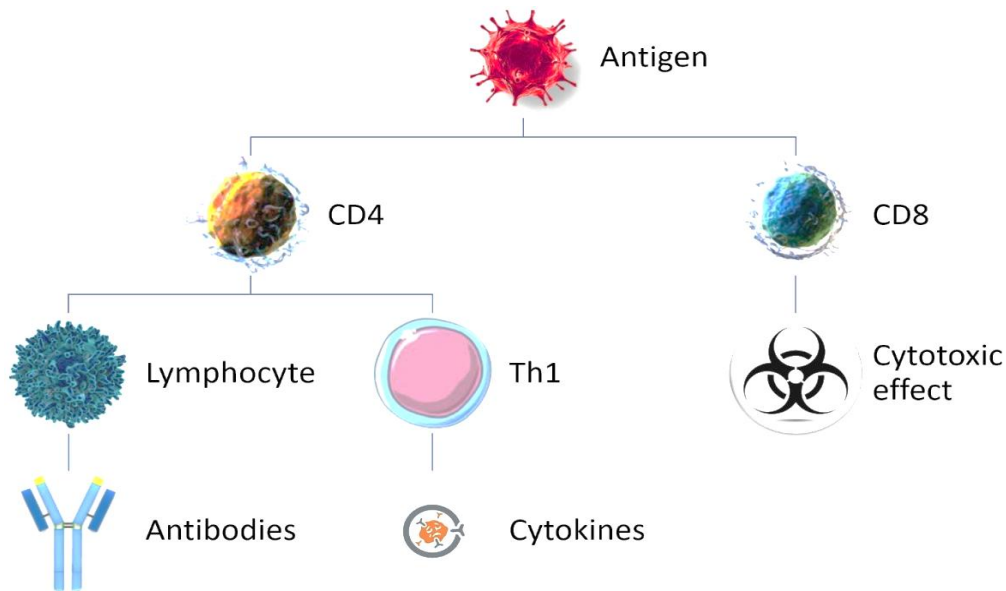


Fig. 2. Adaptive immune response to the presence of viruses. The adaptive immunity comprises B lymphocytes and their products (like cytokines and antibodies) and T-lymphocytes (CD4+ & CD8+)

Following attachment, transmembrane protease serine 2 (TMPRSS2), serine protease, activates the cleavage of spike protein then furin, protease, releases the fusion peptide of the spike and via endosomes, promote entry of the virus to the inside of the cells [37]. Viral infection enhances the regulated cell death, which causes proinflammatory cytokines and chemokines to be stimulated and inflammatory cells to be recruited. The virus itself, on the other hand, induces increased lymphocyte apoptosis (CD3, CD4, and CD8 T-cells) resulting in lymphocytopenia and compromised lymphocyte function ends in rapidly progressive hypercytokinemia described as cytokine storm [38].

This disorder is close to secondary hemophagocytic lymphohistiocytosis or macrophage activation syndrome, a widely recognized finding in intense viral infections marked by increased plasma concentration of IL-6, IL-2, IL-7, CXC-chemokine ligand 10 (CXCL10), TNF, MCP-1, MIP1 and some other proinflammatory agents. This is correlated with presence of acute respiratory distress syndrome (ARDS) and multi-organ failure [39].

4. WHAT HAPPENS WHEN TWO PANDEMICS COLLIDE?

We cannot turn a blind eye on obesity being a pandemic in its own area, but what happens when these two catastrophes co-exist in one patient?

A clear correlation of worse health results in COVID-19 disease with overweight, even in the lack of other comorbidities, has been shown by recent published findings. In a French center study, obese patients, body mass index (BMI) > 30 kg/m² and extreme obese individuals, BMI > 35 kg/m², were observed in 47.6% and 28.2% of severe cases, respectively, while the need for ventilation increased in diabetic and hypertensive cases [40]. Petrilli et al. [41] found that BMI > 40 kg/m² was a significant risk factor for hospital admission, odds ratio is 6.2, in New York City 's academic health system [41]. Increased severity of both disease and secondary bacterial infections and decreased vaccine effectiveness have been shown in several studies on IAV infection in obese mice [42].

The extreme presentation of COVID-19 is described by the unregulated increase in the production of soluble inflammatory cytokines, an unusual systemic inflammatory response and is

often coupled with ARDS recorded in up to 20% of patients with COVID-19 [43,44].

The "cytokine storm" is considered as a popular complication during virus infection and its incidence rate ranges from 3.7% to 4.3%. [45]. It was found to be the main cause of morbidity in subjects with elevated IL-6 and other cytokines after infection with SARS-CoV and MERS-CoV [13,46]. Cytokine storm is characterized by extremely elevated blood concentration of IL-6, TNF-alpha, interferon- γ inducible protein 10 (CXCL10), (granulocyte colony-stimulating factor) G-CSF, MCP1, MIP1-alpha, IL-2 and IL-7 [45-47] (Fig. 3). SARS-CoV-2 can also infect dendritic cells, macrophages and monocytes, that leads to their activation and secretion [48]. On the other hand, obese individuals are already suffering from chronic inflammatory condition, which is preceded by increased inflammatory cytokines, indicating that these persons with elevated inflammatory cytokines and dysfunctional immune response are more vulnerable to this serious condition. An increased severity of obese individuals infected with the H1N1 virus has been reported in the clinical studies [49-51]. This will require the intensive monitoring and therapeutic treatments for these subjects. A delayed and blunted immune response has been shown to occur in obese mice, possibly due to decreased interferon (INF), adaptive cellular response and antibody-mediated response. Serial passaging of a human H1N1 influenza A virus (IAV) in diet-induced obese mice or through genetically obese mice contributes to a more severe illness with an increased infectivity and morbidity. Deep-sequencing viruses detected many mutations in obese host-passaged viruses and a dysfunction of the interferon response is strict for production of stronger IAV strains. These results are not restricted by the viral subtype and are observed in human studies as well. In normal bronchial epithelial cells that derived from obese individuals, decreased INF response and increased replication of the influenza virus have been identified [52-54].

Adaptive immunity is also negatively affected by obesity, a drop in naive CD4-positive T cells, an imbalance of CD4-positive T helper cells towards Th17 and Th22 pro-inflammatory subsets in persons with COVID-19, with low peripheral counts of CD4 and CD8-positive T cells and with a higher proportion of Th17 pro-inflammatory cells [34,55] (Fig. 4). Another significant issue is

physical inactivity in obese patients. Regarding lean patients, sedentary or decreased physical activity is characteristic of obese individuals. Decreased physical activity per se hinders the immune response to microbial agents, including activation of macrophages and inhibition of proinflammatory cytokines [56].

Exercise is positively correlated with beneficial outcomes in metabolic health (diabetes, obesity and metabolic syndrome) and immunologic health (levels of immune activation, effectiveness of vaccination and immune senescence); exercise strategies have shown the propensity to minimize the complications via modulation of the inflammation, enhancing the immunity and improving the outcomes of vaccination in elderly [57].

5. CAN IMMUNO-MODULATORY THERAPY PLAY A ROLE IN TREATING COVID-19?

First, before talking about potential immuno-modulatory agents, we have to mention that exercise can be effective non-pharmacological

interventions [58]. Immuno-modulators have the potential to inhibit cytokines and treat the cytokine storm. These agents are often prescribed to enhance the immune response against infectious diseases, however, morbidity and mortality in severe COVID-19 is associated with hyperinflammation and interfering with cytokine signaling using immunomodulatory strategies may significantly reduce hyperinflammation in these patients. In obese patients, anti-IL-1 and anti-IL-6 agents have shown promising results in severely ill patients [59].

In addition, to modulate dysregulated immune response and repair damaged tissues created by the new COVID-19 virus, mesenchymal stromal cells (MSCs) may be considered. For tissue repair, anti-inflammation and immune regulation, MSC regeneration is beneficial [15,59] (Fig. 5). There are numerous studies on limited case numbers of COVID-19 cases treated with umbilical cord derived MSCs (UC-MSCs). It has been reported that, UC-MSCs treated patients showed an improvement in the clinical criteria including biomarkers of inflammation, tissue damage and oxygen saturation [60-62].

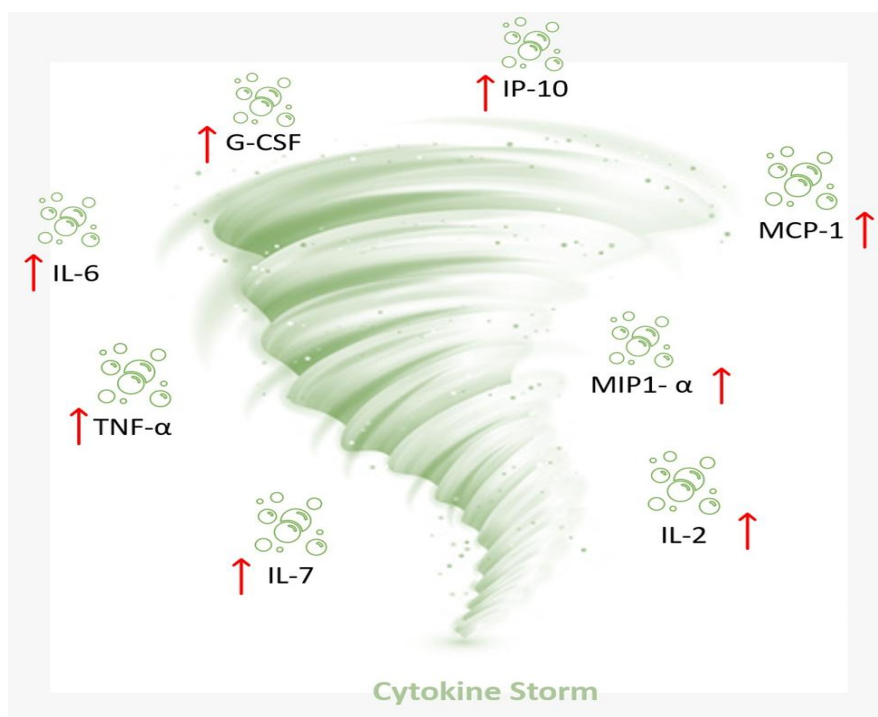


Fig. 3. Immune modulators in cytokine storm. When a cytokine storm has arisen, conventional therapeutics may not be sufficient. Strategies to combat this cytokine storm have included compounds that target fundamental immune pathways, such as the chemokine network leading to a downregulation of the cytokine storm, reducing the risk of tissue damage and allowing time for conventional therapies to target the pathogen directly

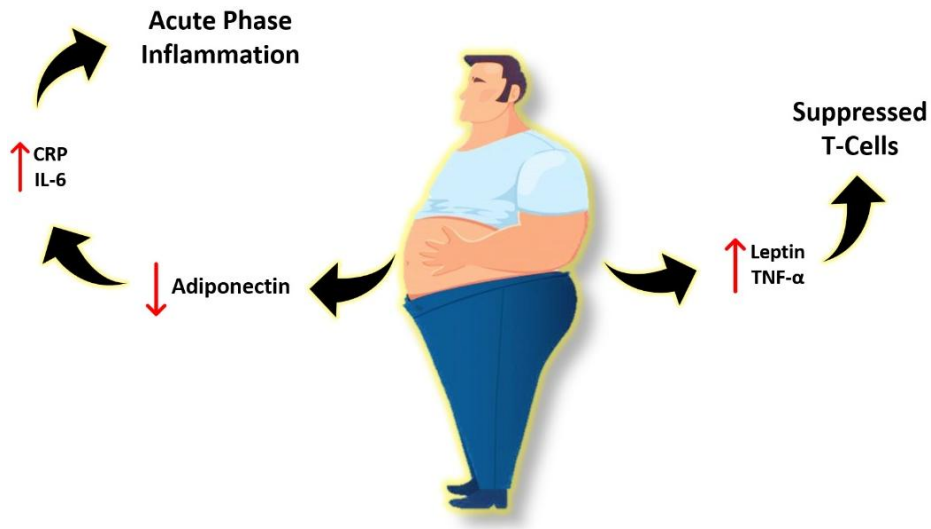


Fig. 4. Effects of adipose tissue on the immune modulators in obese subjects. Obesity causes a state of inflammation and this causes the immune system to become compromised. Chronic inflammation is a serious issue and can lead to the development of minor and serious illness and conditions

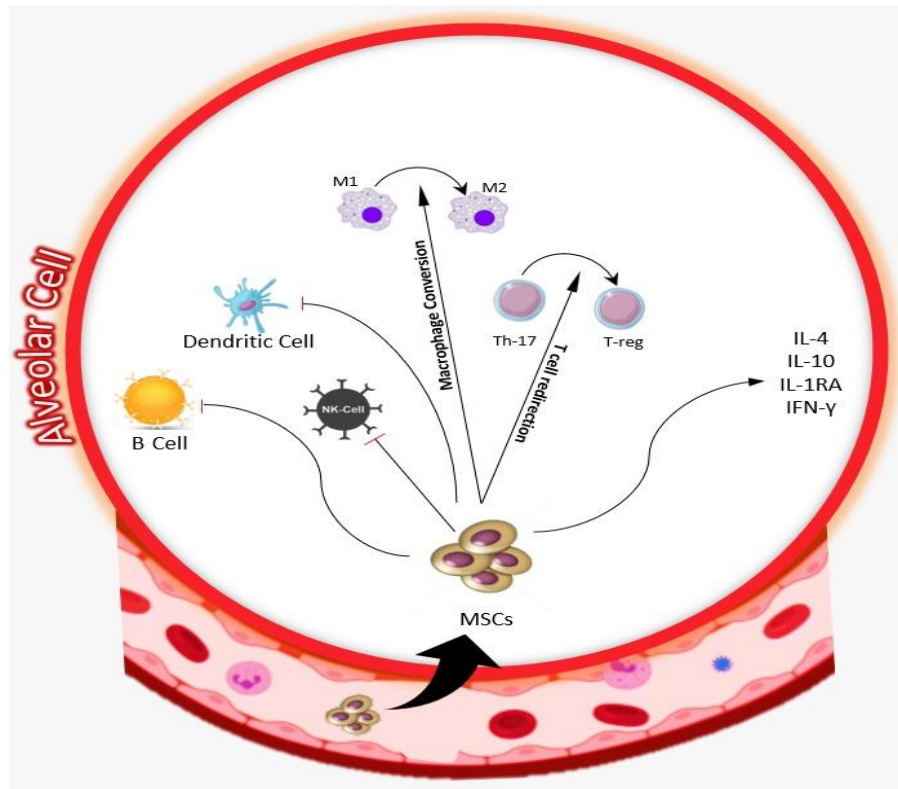


Fig. 5. How mesenchymal stromal cells (MSCs) are combating cytokine Storm in COVID-19 patients? MSCs may be considered to modulate dysregulated immune response and repair damaged tissues created by the new COVID-19 virus

6. CONCLUSION

Various studies show a correlation between COVID-19 and obesity. Obese patients have a longer period of stay in the hospital as well as a more severe clinical picture when compared with lean patients. It has become as a significant risk factor for worse outcomes of COVID-19. The measurement of body mass index, waist circumference and glucose levels should be added to the routine assessments done in hospital settings for obese COVID-19 patients. Exercise and increased Physical activity are important to combating the obesity pandemic but with the social distancing and social isolation it might be challenging to achieve the required moderate physical activity.

There are major gaps in information regarding the effect of dietary components on COVID-19 related immune response and under the background of overweight. To this end, we should be vigilant and proceed with sound nutritional evidence.

FUTURE RESEARCH AND DIRECTIONS

To determine the best treatment strategies for obese subjects, it is important to conduct epidemiological studies to identify the impact of obesity on COVID-19 severity and mortality rates. Large clinical trials are required to assess the effectiveness of immune-modulatory agents in obese patients. Exercise regimens adapted for social distancing and isolation should be outlined for obese subjects and lean subjects alike. Moreover, personalized immunonutrition for obese patients should be considered to reduce the risk of infections and the disease course in COVID-19 patient.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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